A flux of the reds: evolution of active management of the third stage of labour

T F Baskett FRCS FRCOG

J R Soc Med 2000;**93**:489–493 JOINT MEETING SECTIONS OF OBSTETRICS & GYNAECOLOGY AND HISTORY OF MEDICINE, 11 JANUARY 2000

Haemorrhage remains in the top five causes of maternal death in the UK and other countries, both developed and developing[1]. In the developing world at least one woman dies in childbirth every minute, of whom 15–25% will die from postpartum haemorrhage.

The uterus is composed of a unique interlacing network of muscles fibres. The blood vessels that supply the placental bed pass through this latticework of uterine muscle. After delivery of the infant, when the placenta separates from the uterine wall, these fibres contract and constrict the blood vessels. This blood-saving mechanism is known as the 'living ligatures' or 'physiological sutures' of the uterus. It is a superbly efficient method of haemostasis and one of the anatomical and physiological marvels of nature. Indeed, so-called active management of the third stage of labour is really the pharmacological enlistment of these living ligatures so that they are brought into play in all cases after delivery of the infant. The fact that contraction of the uterus is necessary to prevent or stop bleeding after separation of the placenta has been known for centuries, so that attempts to find drugs that would cause these contractions was a logical quest.

In ancient Egyptian medicine there is reference to drugs that were used to promote uterine contraction, either to speed labour or to stem haemorrhage after delivery. The Ebers Papyrus, from approximately 1500 BC, lists potential oxytocics including hemp in honey, celery in milk, juniper berries and fly excrement[2] (the last features in many ancient pharmacopoeias).

Dioscorides was a physician and surgeon who lived in the 1st century AD and may have served with Nero's army. During his travels, he studied the medicinal use of plants and summarized the findings in his epic work *De Materia Medica*, upon which the therapeutic practice of Western countries was largely based until the 17th century. Dioscorides attributed oxytocic properties to the cyclamen plant, which was said to be effective even if the woman walked over the root or tied it around her body: 'They say that if a woman great with childe doe goe over ye roote, that shee doth make abortion, and being tyed about her it doth hasten the birthe'[3]. In the early 17th century, John Gerard was Royal Herbalist and Curator of the College of Physicians Physic Garden in London. His book on the medicinal properties of herbs, *The Herbal or General History of Plants*, was the standard text of the day. Gerard's *Herbal* outlined the oxytocic properties of the plant chervil. He invoked the teaching of Dioscorides and noted that 'the root drunk in wine . . . bringeth downe the menses and secondines . . .'[4].

In the 17th and 18th centuries the approach to postpartum haemorrhage in Europe and Britain is best summarized by the teaching of William Smellie. He was born in Lanark, served a medical apprenticeship in Glasgow, and practised in Lanark for 19 years before moving to London. From the outset he had an affinity for obstetrics and kept a record of all his cases, which later formed part of his three volume *Treatise on Midwifery*. In a sad but beautifully written and precise description, Smellie outlined the spectre of hypovolaemic shock associated with postpartum haemorrhage[5].

> 'This hazardous haemorrhage is known by the violence of the discharge, wetting fresh cloths as fast as they can be applied; from the pulse becoming low and weak, and the countenance turning pale; then the extremities grow cold, she sinks into faintings and, if the discharge is not speedily stopped, or diminished, is seized with convulsions which often terminate in death.'

In his *Treatise*, Smellie clearly attributed the haemorrhage to failure of uterine contraction: 'The dangerous efflux is occasioned by everything that hinders the emptied uterus from contracting . . .'. He noted that the uterus must be kept contracted to stop the blood flowing into the relaxed vessels, showing that he understood the haemostatic mechanism or living ligatures of uterine contractions: ' . . . in these cases such things must be used as will assist the contractile power of the uterus, and hinder the blood from flowing so fast into it and the neighbouring vessels . . . [5].

ERGOT

The modern era of oxytocic drugs started with ergot, the name being derived from the French *argot*, meaning a cock's spur—because of the physical resemblance of the spurs of the fungus *Claviceps purpurea* as it grows on the ear of the grain. Ergotism was caused by eating rye bread

Department of Obstetrics and Gynaecology, Dalhousie University, 5980 University Avenue, Halifax, Nova Scotia B3J 3G9, Canada

contaminated with the fungus ergot. Epidemics of the disease have occurred for at least 1000 years and were related to wet seasons and damp crops which favoured growth of the fungus. The last major epidemic was in Russia in 1938. Most epidemics were of the gangrenous type, in which the toxin caused progressive and permanent narrowing of the arteries. A less common variety of ergotism was the convulsive type, affecting mainly the central nervous system. The difference between the two is partly explained by the variety of alkaloids, including lysergic acid, produced by different strains of the fungus. During epidemics of ergotism, it was observed that women would miscarry; therefore midwives reasoned that ergot must cause uterine contractions and started to use it for prolonged labour with inefficient uterine contractions. It came to be called *pulvis ad partum* (the powder of birth).

The first documentation of ergot to stimulate uterine contractions was by Adam Lonicer in his 1582 herbal book, or *Kräuterbuch*, as 'a proved means of inducing pains of the womb'. He noted that the ergot spurs in diseased rye 'are held to be a special medicine for women in labour, and for the purpose of awakening the pains three of the spurs are swallowed'[6]. It is noteworthy that three ergot spurs contain about 0.5 mg ergometrine, the dose often used for the treatment of postpartum haemorrhage. The first report of ergot in a medical journal was by Paulitzky in 1787, describing its uterine effect as 'more rapid and powerful than any other known drug'[7].

John Stearns from New York is credited with making the use of ergot in obstetrics more widespread in the English speaking world. Apparently, he learned of ergot from a midwife in his rural area of New York—'an ignorant Scottish midwife', as he put it. In 1807, he wrote a letter to a colleague which was subsequently published in the *Medical Repository* of New York in 1808[8]. As he pointed out, '. . . it expedites lingering parturition . . . . The pains induced by it are peculiarly forcing . . . . In most cases you will be surprised with the suddenness of its operation'. This last observation was a key point, to which I will return later. Initially, ergot was used to augment uterine contractions in non-progressive labour. A drawback was the unpredictable and sometimes sustained and very forceful contractions, which could result in asphyxia of the fetus and stillbirth, or even rupture of the uterus and death of the mother. In a later (1822) publication, Stearns was to emphasize these potential complications and talked of the 'necessity of extreme caution'. He also emphasized its use for postpartum haemorrhage: 'In patients liable to haemorrhage, immediately after delivery . . . ergot may be given as a preventive a few minutes before the termination of the labour'[9]. Unfortunately, others used ergot less thoughtfully and its administration caused many perinatal and maternal deaths. In 1813, Oliver Prescott of Massachusetts was among the first to sound the alarm about the risks of ergot given before delivery of the infant. He did, however, confirm the great benefits of ergot given after delivery, for the prevention and treatment of postpartum bleeding. Indeed, he was the first to suggest the use of a prophylactic oxytocic given to prevent postpartum haemorrhage—the forerunner of modern active management of the third stage of labour[10].

> 'The uniform operation of the ergot to restrain uterine haemorrhage . . . has frequently been prescribed, a little previous to the birth of the child, or immediately after, to patients who have been accustomed to flow immoderately, at such times, and it has always proved an effectual preventive.'

Ergotinine, ergotoxine, ergotamine

By 1822, the great increase in the number of stillbirths attributable to ergot was crystallized in a famous quote from David Hosack: 'The ergot has been called *pulvis ad partum*; as it regards the child, it may with almost equal truth be denominated the *pulvis ad mortem*'[11]. Towards the latter half of the 19th century the administration of ergot before delivery was largely abandoned and its use for the treatment of miscarriage and postpartum haemorrhage was emphasized. With the crude ergot preparation the oxytocic action was so variable that dosage and safety margins could not be defined; thus by the late 19th and early 20th century, many laboratories started work on analysis of the alkaloids contained in ergot. The first three alkaloids of ergot to be discovered were ergotinine in 1875[12], ergotoxine in 1906[13] and ergotamine in 1920[14]. The last two proved to have oxytocic properties and became the standard medications for this purpose.

One of the first advocates for active management of the third stage of labour in the UK was a respected obstetrician from Edinburgh, Berry Hart. In the 1912 edition of his *Guide to Midwifery*, he advocated the routine use of ergotine with delivery of the infant's head as a preventive against postpartum haemorrhage[15].

> 'When the child has been born it is a good plan to give a hypodermic of ergotine into the patient's upper hip. . . . I advise that it should be given in all cases after the head is born, and that one should not wait for haemorrhage before injecting it.'

All of the work on the analysis of ergot alkaloids had been conducted in laboratories, with no clinical trials other than subsequent observation to suggest they were effective. In 1932, the therapeutic trials committee of the Medical Research Council, headed by Sir Henry Dale, approached

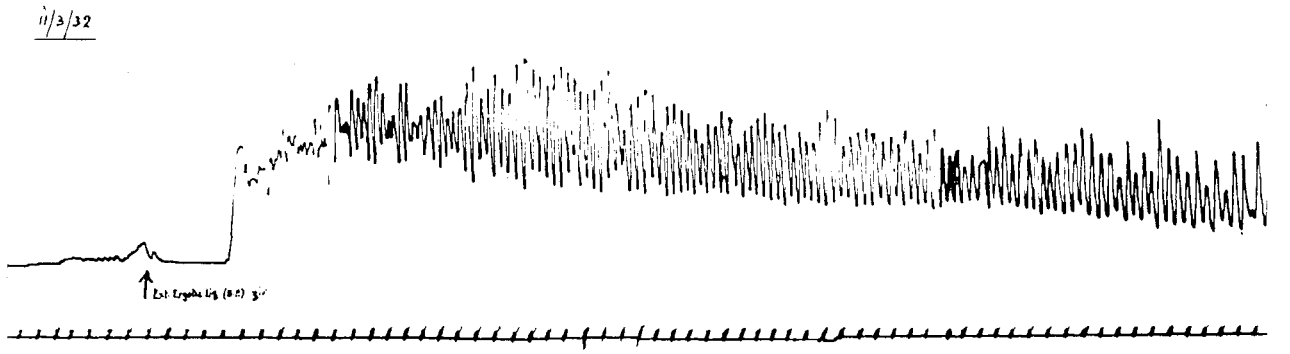

Figure 1 **Kymograph tracing 11 March, 1932, showing the 'John Stearns effect' of aqueous extract of ergot (Chassar Moir)**

the professor of obstetrics, F J Browne, of University College Hospital, London, to consider clinical trials. Browne entrusted this work to Chassar Moir, at that time registrar in Browne's department but later to be appointed to the first Nuffield Chair of Obstetrics and Gynaecology at Oxford University (which he held for 30 years). Moir's first task was to find a means of objectively measuring the clinical efficacy of oxytocic drugs. On the basis of previous work in Germany, and in London by Bourne and Burn, he devised a technique of measuring intrauterine pressure with a small balloon attached to a manometer with the tracing recorded on a slowly revolving drum[16–18]. Moir was able to find or adapt most of his equipment from existing material in the hospital and, as he was later to recount, his only expense was one shilling for some tubing and five shillings for an alarm clock which he modified to allow him to add minute markings to the kymograph charts[19]. He was also to remark that this economy was a source of pleasure to his 'Scottish inheritance'. At that time, routine care of women after delivery included a pelvic examination on the 6th or 7th day, before discharge. Moir reasoned that insertion of the balloon into the uterus at this stage would subject the patients to little extra discomfort. He was aware of possible hostility to such clinical research and kept his equipment in a small room adjacent to the ward and connected to the patient by tubing run out through the window. This was found to be unsatisfactory so he later drilled a hole through the wall between the two rooms. His first experiment was a great success when he recorded the uterine contractions associated with breastfeeding, known to be due to the release of hormone from the posterior pituitary in response to suckling[19].

Ergometrine

Experiments with the then-known alkaloids of ergot—ergotoxine and ergotamine—also showed uterine contractions but they were much slower to take effect and with quite prolonged and variable delay. This was not the effect that Moir had hoped for. He remembered John Stearns' observation—'you will be surprised by the suddenness of its operation'. Obviously, the currently isolated alkaloids of ergot did not produce this desired quick response, which Chassar Moir came to call the 'John Stearns effect'. The standard pharmacopoeia preparation of ergot was the aqueous extract, largely dismissed by pharmacologists because it did not contain any of the then-known alkaloids. In March 1932, Moir administered the standard dose of aqueous ergot by mouth. Within a few minutes he noticed dramatic, vigorous, and sustained oscillations on the recorder (Figure 1). He was amazed and delighted; he had discovered the 'John Stearns effect'. He published this finding[20] and the search for the unidentified active constituent of ergot, which might then be injected for quick effect, began in earnest. Sir Henry Dale enlisted his chief research chemist, Harold Dudley. The task was daunting since there were dozens of chemical fractions of ergot, and to assess the oxytocic properties each fraction had to be given to Moir and tested on postpartum patients. This went on for three years until, in early 1935, yet another pure crystallized substance was forthcoming from Dudley and this one proved to be a winner. On 9 February 1935 a beautiful tracing showed the 'John Stearns effect' (Figure 2).

Five weeks later, in the *British Medical Journal* of 26 March, 1935, Dudley and Moir published their findings[21]. Almost simultaneously from three other centres—Chicago[22], Baltimore[23] and Switzerland[24]—the isolation of a new water-soluble extract of ergot was announced. A concomitant publication by Dudley also provided the method of preparation in full and there were to be no patent rights or involvement with proprietary interests[25]. At Dale's suggestion they named it ergometrine. The Americans called their preparation ergonovine and the Swiss used the name ergobasine. All three were subsequently shown to be chemically identical. Thus, three years of research by one chemist and one clinical investigator, aided by six shillings' worth of recording equipment, were to produce and make instantly available a simple, safe, and effective drug that was, in the succeeding half century, to save thousands of

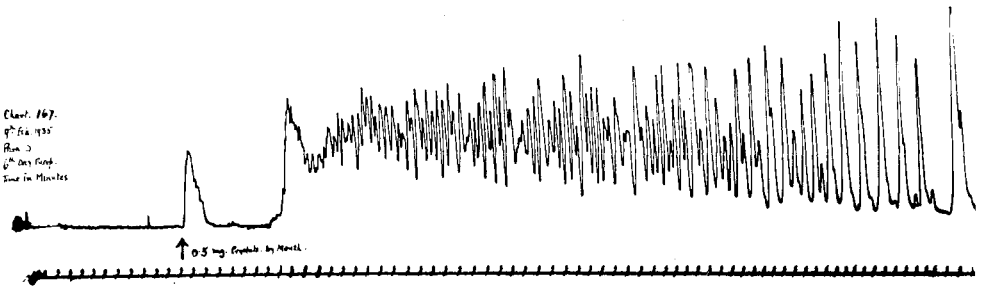

Figure 2 **Kymograph tracing 9 February, 1935, showing the oxytocic effect of ergometrine (Chassar Moir)**

lives worldwide. Many years later Chassar Moir was to say of ergometrine: 'Reckoned in the saving of human life, places it among the enduring achievements of medical science'[19]. An achievement in which, it should be added, he played a very important role.

No sooner had ergometrine become available than F J Browne embarked upon a study at University College Hospital, London. This was not reported until 1947 when J D S Flew mentioned this study in a paper read before the RSM and later published in the *Proceedings*[26]. He reported, almost *en passant*, that 500 consecutive cases were treated with 0.5 mg ergometrine given intramuscularly when the head delivered. He did not report the blood loss or cases of haemorrhage, but noted that no patient required manual removal and there were no cases of uterine inversion, which were both theoretical worries expressed about the use of ergometrine.

Edward Davis of Chicago, who had isolated ergometrine almost simultaneously with Moir and Dudley, advocated in 1940 the routine administration of 0.2 mg ergometrine intravenously with delivery of the head[27]. Two years later he and his colleague Melbourne Boynton reported on 2000 cases so treated, noting a considerable reduction in blood loss and postpartum haemorrhage[28]. Furthermore, the need for manual removal of the placenta was no greater than in patients whose third stage was managed traditionally. This most active management of the third stage of labour was never really accepted in the United States. Despite evidence to the contrary, there has been widespread belief that oxytocics given with delivery of the infant increased the risk of retained placenta; thus, common practice in the United States has been to await delivery of the placenta and then give a prophylactic oxytocic.

In 1949 David Shaw, from Manchester, reported an observational study showing that the use of ergometrine 0.5 mg given as the head crowned reduced the duration of the third stage of labour as well as blood loss and need for blood transfusion[29]. He also observed that retained placenta and the need for manual removal were not increased by the use of ergometrine. In 1951, Doreen Daley from Carlshalton was the first to conduct a comparative study of the routine administration of 0.5 mg ergometrine to normal parturients. 1000 women were studied—490 study patients and 510 controls[30]. The study group received active management with 0.5 mg ergometrine given intramuscularly as the head crowned. Blood loss and duration of the third stage of labour were significantly reduced, and the rate of postpartum haemorrhage was lowered by about 40% (9.2% versus 15.7%). The incidence of retained placenta did not differ between the two groups.

OXYTOCIN

A further landmark in the evolution of safe oxytocic drugs was achieved in 1953 by Vincent Du Vigneaud, of Cornell University Medical College. He identified the structure of oxytocin and was able to synthesize the hormone[31]. With the development of effective and safe oxytocic drugs active management of the third stage of labour became routine in many hospitals. By the 1980s several randomized controlled trials and their meta-analyses confirmed the effectiveness of active management of the third stage of labour in reducing postpartum haemorrhage and the need for blood transfusion by 40–50%[32–34]. These trials showed both oxytocin and ergometrine to be effective. Ergometrine, however, has more side-effects, including nausea, vomiting and hypertension. Thus, although ergometrine has a long and noble history in the prevention and management of postpartum haemorrhage, oxytocin has become the drug of first choice for active management of the third stage of labour[35,36].

PROSTAGLANDINS

By the 1970s the prostaglandin F2α series was delineated by Sune Bergstrom, among others[37]. The 15-methyl analogue of prostaglandin F2α has proved to be the most useful in the management of postpartum haemorrhage. It has a very strong uterotonic effect and lacks many of the other undesirable smooth muscle stimulation effects of the parent compound[38]. However, this prostaglandin is much more expensive than oxytocin and ergometrine and therefore not

suitable for routine use in active management of the third stage of labour. The orally administered prostaglandin E_1 analogue misoprostol shows promise as a cheap oxytocic for prevention of postpartum haemorrhage[39]. It may facilitate the wider use of active management of the third stage of labour in the developing world—perhaps even by untrained attendants or family members—and so reduce the carnage of postpartum haemorrhage.

REFERENCES

1 Department of Health. *Why Mothers Die: Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–96*. London: Stationery Office, 1998

2 Nunn JF. *Ancient Egyptian Medicine*. London: British Museum Press, 1996: 193–5

3 Gunther RT. *The Greek Herbal of Dioscorides*, book 2. London: Hafner Publishing 1968:203

4 Gerard J. *The Herbal or General History of Plants* (complete 1633 edition as revised and enlarged by Thomas Johnson). New York: Dover Publications, 1970:1040

5 Smellie W. *A Treatise on the Theory and Practice of Midwifery*. London: D Wilson, 1752:402–4

6 Moir JC. The history and present day use of ergot. *Can Med Assoc J* 1955;**72**:727–34

7 Paulitsky F. Pulvis ad partum aus dem Mutterkorn. *Neues Mag für Arzte* 1787;**9**:44

8 Stearns J. Account of the pulvis parturiens, a remedy for quickening childbirth. *Med Repository NY* 1808;**11**:308–9

9 Stearns J. Observations on the secale cornutum or ergot, with directions for its use in parturition. *Med Rec* 1822;**5**:90

10 Prescott O. *A Dissertation on the Natural History and Medical Effects of the Secale Cornutum, or Ergot*. Andover: Flagg & Gould, 1813:14

11 Hosack D. Observations on ergot. In: *Essays on Various Subjects of Medical Science*. New York: 1824:295–301

12 Tanret C. Sur la presence d'une nouvelle alkaloide, l'ergotinine, dans seigle ergoté. *CR Acad Sci* 1875;**81**:896–7

13 Barger G, Carr FH, Dale HH. An active alkaloid from ergot. *BMJ* 1906;**ii**:1792

14 Stoll A. Zur Kenntins der Mutterkorn alkaloide. *Verhand der Schweiz Naturf Ges* 1920;**6**:190

15 Hart DB. *Guide to Midwifery*. London: Heinemann, 1912:220

16 Schatz F. Beitrage zur physiologischen Geburtskunde. *Arch Gynakol* 1872;**3**:58–9

17 Rübsamen W. Klinisch-experimentelle Untersuchungen über die Wirksamkeit der Wehenmittel in der Nachgeburtsperiode. *Munch Med Wschr* 1913;**12**:627–30

18 Bourne A, Burn JH. The dosage and action of pituitary extract and ergot alkaloids on the uterus in labour, with a note on the action of adrenalin. *J Obstet Gynaecol Br Emp* 1927;**34**:249–68

19 Moir JC. The obstetrician bids, and the uterus contracts. *BMJ* 1964;**i**:1025–9

20 Moir JC. The action of ergot preparations on the puerperal uterus. *BMJ* 1932;**i**:1119–22

21 Dudley HW, Moir C. The substance responsible for the traditional clinical effect of ergot. *BMJ* 1935;**i**:520–3

22 Davis ME, Adher FL, Rogers G, Kharasch MS, Legault RR. A new active principle in ergot and its effects on uterine motility. *Am J Obstet Gynecol* 1935;**29**:155–67

23 Thompson MR. The active constituents of ergot. A pharmacological and chemical study. *J Am Pharm Soc* 1935;**24**:185–96

24 Stoll A, Burckhardt E. L'ergobasine, nouvel alkaloide de l'ergot de seigle, solubile dans l'eau. *Bull Sci Pharm* 1935;**42**:257–66

25 Dudley HW. Ergometrine. *Proc R Soc Lond* 1935;**118**:478–84

26 Flew JDS. Discussion on the management of the normal third stage of labour and of haemorrhage therein. *Proc R Soc Med* 1947;**40**:370–1

27 Davis ME. Postpartum hemorrhage. *Am J Surg* 1940;**48**:154–63

28 Davis ME, Boynton MW. The use of ergonovine in the placental stage of labor. *Am J Obstet Gynecol* 1942;**43**:775–90

29 Shaw DAF. Oxytocic drugs in the third stage of labour. *J Obstet Gynaecol Br Emp* 1949;**56**:833–7

30 Daley D. The use of intramuscular ergometrine at the end of the second stage of normal labour. *J Obstet Gynaecol Br Emp* 1951;**58**:388–97

31 Du Vigneaud V, Ressler C, Swan JM, Roberts CW, Katsoyannis PG, Gordon S. The synthesis of an octapeptide with the hormonal activity of oxytocin. *J Am Chem Soc* 1953;**75**:4879–80

32 Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial; active versus physiological management of third stage of labour. *BMJ* 1988;**297**:1295–300

33 Prendiville WJ, Elbourne DR, Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1988;**95**:3–16

34 Elbourne DR, Prendiville WJ, Chalmers I. Choice of oxytocic preparation for routine use in the management of the third stage of labour: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1988;**95**:17–30

35 Soriano D, Dulitzki M, Schiff E, Barkai G, Mashiach S, Seidman DS. A prospective cohort study of oxytocin plus ergometrine compared with oxytocin alone for prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1996;**103**:1068–73

36 Nordström L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. *Br J Obstet Gynaecol* 1997;**104**:781–6

37 Bergstrom S, Ryhag ER, Samuelson B, Sjovall J. The structure of prostaglandin E, F_1 and F_2. *Acta Chem Scan* 1962;**16**:501–2

38 Annathasubramanim L, Kuntal R, Sivariman R, Raghaven KS. Management of intractable postpartum haemorrhage secondary to uterine atony with intramuscular 15-methyl $PGF_2\alpha$. *Acta Obstet Gynecol Scand* 1988;**145**(suppl):17–19

39 El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1997;**104**:336–9